

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
6 May 2005 (06.05.2005)

PCT

(10) International Publication Number
WO 2005/039532 A1

- (51) International Patent Classification⁷: **A61K 9/10**,
A61P 35/00, A61K 31/167, 31/07
- (21) International Application Number:
PCT/EP2004/011236
- (22) International Filing Date: 8 October 2004 (08.10.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI2003A002019 17 October 2003 (17.10.2003) IT
- (71) Applicant (for all designated States except US): **FIDIA FARMACEUTICI S.p.A.** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **MENEGATTI, Enea** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT). **CORTESI, Rita** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT). **ESPOSITO, Elisabetta** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT). **BELLATO, Pierangelo** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT). **GENNARI, Giovanni** [IT/IT]; Via Ponte della Fabbrica, 3/A, I-35031 Abano Terme (IT).
- (74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Plinio, 63, I-20129 Milano (IT).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MICROEMULSIONS OF RETINOIDS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: Disclosed are water-in-oil (W/O) microemulsions containing as active ingredient a retinoid, a phospholipid emulsifier, and possibly hyaluronic acid or salts thereof.

WO 2005/039532 A1

MICROEMULSIONS OF RETINOIDS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to water-in-oil (W/O) microemulsions containing a retinoid as active ingredient, a phospholipid emulsifier, and possibly hyaluronic acid or salts thereof.

BACKGROUND TO THE INVENTION

5 Retinoids are defined as a series of compounds which are natural derivatives or synthetic analogues of vitamin A. The role of vitamin A as an essential nutrient was recognised as early as 1913, since which time a great deal of research has been conducted on the product. Wolbach and Howe (J. Exp. Med. 42: 753,1925) first described the histopathological epithelial
10 variations caused by vitamin A deficiency in 1925. This led to the identification of retinol and other natural analogues which began to be used, on a purely empirical basis, as chemopreventive agents of neoplastic transformation.

 The role of retinoids in oncological chemoprevention was endorsed by
15 the publication of various epidemiological studies which demonstrated that a regular vitamin A intake was significantly correlated with a lower incidence of tumours, especially lung cancer (Zeigler R.G. et al., Cancer Causes and Control 7: 157-177, 1996; Krishnan K. et al., Primary Care 25: 361-382, 1998).

20 Only some of the over 4000 retinoids tested to date have a sufficiently favourable therapeutic efficacy/toxicity ratio to allow their clinical use. The relatively recent discovery of nuclear receptors for retinoic acid (which belong to two distinct types, called RAR and RXR) has considerably improved knowledge of their action mechanisms.

25 Numerous clinical trials have been conducted with retinoids, many of

them on skin diseases such as lichen planus and leucoplakia which, due to the high frequency of neoplastic transformation, are classed as pre-cancerous lesions (Hong W et al., N. Engl. J. Med 315: 1501-1505,1986; Lippman S.M et al., N. Engl. J. Med 328: 15-20,1993).

5 At present, the internationally recognised clinical use of the retinoids relates to the treatment of acute promyelocytic leukaemia and skin diseases with a hyperproliferative component such as acne and psoriasis.

Fenretinide (4-hydroxyphenyl retinamide) is a semi-synthetic retinoid which was developed as a chemoprotective agent (Costa A. et al., Ann. N.Y. Acad. Sci. 768: 148-162,1995; Pienta K.J. et al., Am. J. Clin. Oncol. 20: 10 36-39,1997).

Unlike other natural retinoids such as all-trans, 13-cis- and 9-cis-retinoic acid, fenretinide does not induce any systemic catabolism which could interfere with the long-term maintenance of pharmacologically useful plasma 15 concentrations. This characteristic, combined with the low toxicity of the product and its ability to inhibit some phenomena associated with carcinogenesis, provides the rationale for the development of fenretinide as a chemoprotective agent in neoplastic disorders such breast, prostate and bladder cancer.

20 Other phase II trials, conducted on a limited number of subjects, have evaluated the effect of fenretinide on patients suffering from prostate cancer (Pienta K.J. et al., Am. J. Clin. Oncol. 20: 36-39, 1987), melanoma (Modiano M.R. et al., Invest. New Drugs 8: 317-319, 1990) and myelodysplastic syndromes (Garewal H.S. et al., Leukemia Res. 13: 339-343, 1989). However, 25 the results of these studies were rather disappointing, whereas chemoprevention studies conducted on patients suffering from leucoplakia or lichen planus (dermatological lesions which often present neoplastic degeneration) have given promising results (Tradati N. et al., Canc. Letters 76: 109-111, 1994).

In these cases the patients were treated topically, with the result that the fenretinide concentrations reached in the lesion were probably similar to, if not higher than those which have proved active *in vitro*.

At present, topical formulations of retinoids are mainly presented in the form of creams with a fatty base or gels. DE 19946184 describes emulsions of retinoids characterised by a continuous aqueous phase, a mainly non-crystalline viscous oily phase, and a mixture of emulsifiers. Microemulsions of active ingredients which are poorly soluble in water and can be administered by the parenteral, topical or oral route are described in WO 99/56727, EP 211258 and EP 760237.

Topical formulations of retinoids in the form of microemulsions (macroscopically monophasic dispersed systems constituted by at least three components, such as an oily phase, an aqueous phase and a surfactant) are not available. The main chemico-physical properties of microemulsions which characterise their particular structure are transparency, isotropy and thermodynamic stability. As a result of these characteristics, microemulsions are of considerable interest to the pharmaceutical industry. In fact:

- (a) the particular microstructure of microemulsions enables molecules with different chemico-physical characteristics to be solubilised;
- (b) the transparency of the system makes it possible to check that the active ingredients are completely solubilised;
- (c) thermodynamic stability entails major advantages, as the systems obtained are stable for long periods of time.

A further advantage of the topical use of microemulsions is the possibility of increasing the rate of penetration of the active ingredients through the stratum corneum.

Drug release is known to be much faster when gel microemulsions are used rather than conventional formulations (Martini M. et al., J. Pharm. Belg.

39, 348-354, 1984; Ziegenmeyers J. et al., Acta Pharm. Technol. 26, 273-275, 1980; Ziegenmeyers J. et al., Deuxième Congrès International de Technologie Pharmaceutique 3, pp. 235-238, 1980).

5 Phospholipids have been used as emulsifying agents to stabilise microemulsions: phosphatidylcholines in an organic solvent (50-250 mM) form small inverse micelles which, on the addition of water, undergo one-dimensional growth, until the formation of a kind of three-dimensional network consisting of a tangle of long, flexible cylindrical structures (Luisi et al., Colloid Polym. Sci. 268, 356-374, 1990).

10 The presence of water causes a drastic increase in viscosity, leading to the formation of a gelified transparent system, the viscosity of which depends on the content of the aqueous phase. The water content, which is consequently a very important factor in the formation of these particular microemulsions, is expressed by the ratio between the water concentration and the molar lecithin
15 concentration:

$$[W]/[lec] = [\text{molar water concentration}] / [\text{molar lecithin concentration}]$$

The maximum value of $[W]/[lec]$ for each microemulsion depends on the type of organic phase used and the lecithin concentration. The maximum viscosity of lecithin-based gel microemulsions is usually obtained after the
20 addition of less than 10 molecules of water per molecule of lecithin, namely at values of $[W]/[lec] < 10$.

Gel microemulsions based on soy phosphatidylcholine possess all the characteristics of transparency, thermodynamic stability and isotropy typical of microemulsions (Scartazzini R. et al., J. Phys. Chem. 92, 829-833, 1988; Luisi et al., Colloid Polym. Sci. 268, 356-374, 1990; Lawrence et al.,
25 Advanced Drug Delivery Reviews 45, 89-121, 2000).

Phosphatidylcholine is a natural surfactant, and is highly biocompatible (Dreher et al., Skin Pharmacology 9, 124-129, 1996).

Hyaluronic acid (HA) is a heteropolysaccharide composed of alternate residues of D-glucuronic acid and N-acetyl-D-glucosamine. It is a linear-chain polymer with a molecular weight ranging between 50,000 and 13×10^6 Da, depending on the source from which it is obtained and the preparation methods used. It is found in nature in pericellular gels, in the ground substance of the connective tissue of vertebrates (of which it is one of the main components), and in synovial (joint) fluid, vitreous humour and the umbilical cord.

HA plays an important role in biological organisms, as a mechanical support for the cells of many tissues such as skin, tendons, muscles and cartilage.

It is the main component of extracellular matrix, and also performs other functions such as tissue moisturising and cell lubrication, migration and differentiation.

In view of its properties of bio- and mucoadhesion and its tissue compatibility characteristics, hyaluronic acid and its salts, in particular sodium, potassium, magnesium and calcium salts, possibly suitably fractionated and/or derivatised, have been proposed as systems for the release of drugs and the preparation of surgical aids, implants, prostheses and the like.

DESCRIPTION OF THE INVENTION

It has now been found that retinoids can be advantageously formulated in water-in-oil (W/O) microemulsions using phospholipid emulsifiers, in particular soy phosphatidylcholine and soy lecithin, possibly with the addition of hyaluronic acid or salts and fractions thereof.

The microemulsions of the invention provide better bioavailability than conventional formulations.

The oily phase is preferably constituted by alkyl esters of C_{10} - C_{22} fatty acids.

Isopropyl palmitate is particularly preferred.

Retinoids which can be conveniently formulated in the microemulsions

according to the invention include isotretinoin (13-cis-retinoic acid), tazarotene and, in particular, fenretinide.

It has also surprisingly been found that the addition of hyaluronic acid (HA), possibly salified, and in particular sodium hyaluronate or HA
5 derivatives, to microemulsions further increases the bioavailability of the active ingredient.

The HA used in the present invention may derive from any source, such as extraction from rooster combs (EP 0138572), fermentation (EP 0716688), or technological means (Italian patent application no. PD94A000042), and have a
10 molecular weight of between 400 and 3×10^6 Da, in particular between 400 and 1×10^6 Da, and even more particularly between 400 and 200,000 Da.

The HA derivatives which can be used are listed below:

1) HA salified with organic and/or inorganic bases having a molecular weight of 50-730 kDa (EP 0138572) or a high molecular weight
15 (750-1230 kDa, EP 535200);

2) Hyaff: HA esters with alcohols of the aliphatic, araliphatic, cycloaliphatic, aromatic, cyclic and heterocyclic series, with an esterification percentage which may vary, depending on the type and length of the alcohol used (EP 216453);

20 3) Hyadd: HA amides with amines of the aliphatic, araliphatic, cycloaliphatic, aromatic, cyclic and heterocyclic series (EP 1095064);

4) O-sulphated HA derivatives up to the 4th degree of sulphation (EP 0702699);

5) ACP: inner esters of HA (EP 0341745).

25 The fraction known as Hyalastine, a fraction of hyaluronic acid with molecular weights of between 50 and 200 kDa, is preferred.

Hyaluronic acid and its salts act as viscosity agents, and guarantee improved characteristics in terms of stability and bioavailability.

The microemulsions according to the invention may also contain antioxidants and preservatives such as α -tocopherol, alkyl parabens, and other excipients of conventional use.

5 The weight percentage of active ingredient can range between 0.01% and 0.5%, preferably between 0.05 and 0.15%, while the weight percentage of lecithin or phosphatidylcholine is typically between approx. 10% and approx. 15%. The aqueous phase typically constitutes approx. 0.5 to 2% in weight of the total microemulsions. Sodium hyaluronate can be added as viscosity agent in percentages of between 0.001 and 0.01% in weight.

10 The microemulsions according to the invention can be prepared by a process which comprises the addition of a solution of phospholipid emulsifier in the oily phase to the retinoid solution in the same oily phase, and subsequent addition of an aqueous solution possibly containing hyaluronic acid, its salts or derivatives, preservatives, EDTA and other ingredients.

15 **EXAMPLES 1-3: Fenretinide microemulsions**

Preparation method

α -tocopherol is solubilised in a small volume of isopropyl palmitate (IPP). Soy phosphatidylcholine is solubilised in the remaining volume of isopropyl palmitate at 70°C under stirring until a clear, transparent solution is obtained.

20 Propyl paraben is then added, and stirring is continued until solubilisation is complete.

The solution is cooled, the solution of α -tocopherol in isopropyl palmitate is added, and the resulting solution is mixed under gentle stirring.

The active ingredient is solubilised in the resulting solution.

25 Methyl paraben is solubilised in purified water at 80°C to prepare the aqueous phase. The solution is cooled at room temperature, and tetrasodium EDTA and hyaluronic acid sodium salt are solubilised under stirring.

The aqueous solution is added to the isopropyl palmitate oily solution,

and the resulting system which is initially turbid, is maintained under stirring until a clear, transparent emulsion of acquired viscosity is obtained.

Qualitative and quantitative compositions

The compositions of the microemulsions obtained by the method described above, which have different W/[lec] ratios depending on whether they contain sodium hyaluronate, are reported below:

EXAMPLE 1 - IPP2 Hyal ([W]/[lec]: 2).

Constituent	% w/w	Function
Fenretinide	0.05 – 0.10 – 0.15	Active ingredient
Phosphatidylcholine	14.756	Surfactant
Isopropyl palmitate	q.s. for 100	Oily phase
Purified water	0.7644	Aqueous phase
Hyaluronic acid sodium salt (Hyalastine fraction)	0.0072	Viscosity agent
α -Tocopherol	0.10	Antioxidant

EXAMPLE 2 - IPP3C Hyal ([W]/[lec]: 3).

10

Constituent	% w/w	Function
Fenretinide	0.05 – 0.10 – 0.15	Active ingredient
Phosphatidylcholine	14.567 – 14.560 – 14.553	Surfactant
Isopropyl palmitate	q.s. for 100	Oily phase
Purified water	1.1107 – 1.1102 – 1.1096	Aqueous phase
Hyaluronic acid sodium salt (Hyalastine fraction)	0.0108	Viscosity agent
α -Tocopherol	0.10	Antioxidant
Methyl paraben	0.00162	Preservative
Propyl paraben	0.000215	Preservative
Tetrasodium EDTA	0.00108	Complexing agent

EXAMPLE 3 - IPP3C' Hyal ([W]/[lec]: 3).

Constituent	% w/w	Function
Fenretinide	0.05 – 0.10 – 0.15	Active ingredient
Phosphatidylcholine	14.567 – 14.560 – 14.553	Surfactant
Isopropyl palmitate	q.s. for 100	Oily phase
Purified water	1.109 – 1.108 – 1.1096	Aqueous phase
Hyaluronic acid sodium salt (Hyalastine fraction)	0.0108	Viscosity agent
α -Tocopherol	0.10	Antioxidant
Methyl paraben	0.00216	Preservative
Propyl paraben	0.01684	Preservative
Tetrasodium EDTA	0.00108	Complexing agent

EXAMPLE 4: Rheological characterisation

Dynamic viscosity measurements were performed to characterise the gel microemulsions produced; in particular, viscosity measurements were conducted by applying increasing shear rate values, from which the viscosity values at a shear rate of a 70 s^{-1} were extrapolated (measurements conducted at 25°C).

Figure 1 shows the viscosity trend of gel microemulsions based on isopropyl palmitate (IPP) at an active ingredient (fenretinide) concentration of 0.05% w/w, depending on the water content ([W]/[lec] equal to 1, 2 and 3).

The viscosity of IPP1 ([W]/[lec] = 1) and IPP2 ([W]/[lec] = 2) gel microemulsions is considered too low; however, IPP3 gel microemulsions (those with a water content expressed by a [W]/[lec] ratio of 3) are considered to have good viscosity and consistency characteristics for topical application.

Figure 2 shows the viscosity trend of gel microemulsions based on isopropyl palmitate (IPP) which have the same ratio [W]/[lec] (= 3) and concentration as the drug fenretinide (0.05%), but a different

qualitative/quantitative composition, and contain hyaluronic acid sodium salt (Hyalastine fraction) as viscosity agent in order to obtain the viscosity and consistency characteristics considered ideal for the intended uses.

Figure 3 shows the viscosity trend of the microemulsion classed as prototype IPP3C', according to the fenretinide concentration (4HPR), in which slightly inferior viscosity and consistency characteristics are observed as the dose of fenretinide increases.

EXAMPLE 5: Diffusion kinetics of fenretinide

An *in vitro* study was conducted to compare the diffusion or permeation (through a membrane) kinetics of fenretinide in the microemulsions according to the invention with fenretinide in conventional formulations, such as the "ointment base containing cetomacrogol" and "fatty cream base containing cetomacrogol" described in the Italian Official Pharmacopoeia (F.U.), current edition.

"Franz diffusion cells" associated with a cellulose membrane were used to study the diffusion kinetics of fenretinide in the different formulations.

The cell consists of two glass sections, one above the other. The inner diameter of the cell is 1 cm (equal to an area of 0.78 cm²).

The formulation containing fenretinide was placed in the top section, while the bottom section was filled with the receptor phase constituted by methanol, and maintained under constant stirring by means of a magnetic "follower" fitted at the base of the cell.

The membrane, previously moistened with the receptor phase, was placed between the two sections. The two sections of the cell were assembled, taking care to avoid the formation of air bubbles. All the experiments were carried out under the same conditions: shaded from the light, at the temperature of 25°C, the bottom section being thermostated at 32°C, and 4 cells being used in parallel.

Samples of the receptor phase were taken at pre-set intervals (from 30 minutes to 8 hours) using a syringe with a flexible teflon tube; each sample was then replaced with an equal volume of receptor phase.

The samples were analysed for their fenretinide content using reverse-phase HPLC chromatography. The total quantities of fenretinide released per area unit ($\mu\text{g} / \text{cm}^2$) were calculated from the results of the chromatographic analysis.

The tests were repeated in quadruplicate for each formulation. The mean values were then calculated and shown in the graph as a function of time, expressed in hours.

The test points were interpolated with a linear regression calculation, obtaining lines of the type " $y=mx + q$ ". Angular coefficient " m ", which represents the slope of the line, corresponds to test flow " J_s ".

It is known that $J_s = C \times J_n$, where C is the concentration of the drug expressed in mg/ml.

As the fenretinide concentration in all the formulations analysed was 1 mg/ml, " J_s " is equal to " J_n ". " J_n " represents the diffusion coefficient, namely the flow rate at which the drug permeates through the membrane.

Figure 4 shows the diffusion or permeation kinetics of fenretinide (absorption rate) in gel microemulsions IPP3C and IPP3C' (without hyaluronic acid sodium salt, Hyalastine fraction) by comparison with fenretinide in conventional formulations ("ointment base containing cetomacrogol" and "fatty cream base containing cetomacrogol"); the angular coefficients of the lines obtained represent the values of diffusion coefficient " J_n ".

Figure 5 shows the diffusion or permeation kinetics of fenretinide (absorption rate) in the same gel microemulsions containing hyaluronic acid sodium salt (Hyalastine fraction) by comparison with fenretinide in conventional formulations ("ointment base containing cetomacrogol" and

“fatty cream base containing cetomacrogol”).

Figure 6 shows the diffusion or permeation kinetics of fenretinide (absorption rate) in gel microemulsions IPP3C and IPP3C' with or without hyaluronic acid sodium salt (Hyalastine fraction).

- 5 The diffusion (or permeation or absorption) coefficients “J_n” of fenretinide carried in gel microemulsions type IPP3 ([W]/[lec] = 3), in the absence and presence of hyaluronic acid sodium salt (Hyalastine fraction), and in conventional formulations, are set out in the table below:

Formulation	Fenretinide (% w/v)	J _n (µg/cm ² /h)	log J _n
Ointment base, F.U	0.1	0.15	-0.82
W/O cream base, F.U.	0.1	0.50	-0.3
IPP 3 C	0.1	13.43	1.12
IPP 3 C HYAL	0.1	18.47	1.26
IPP 3 C'	0.1	10.22	1.00
IPP 3 C' HYAL	0.1	16.19	1.20

- 10 The following conclusions can be drawn from the test results obtained:

- The kinetics of diffusion or permeation (absorption rate) of fenretinide carried as a gel microemulsion based on phospholipids (soy phosphatidylcholine) are considerably greater than those of the drug when carried in conventional formulations (W/O cream or ointment); the diffusion coefficients “J_n” of fenretinide carried as a gel microemulsion are considerably greater than those obtained with an ointment (approx. 79 times higher) and/or a W/O cream (approx. 24 times higher).
- Surprisingly, the kinetics of diffusion or permeation (absorption rate) of fenretinide carried as a gel microemulsion based on phospholipids (soy phosphatidylcholine) are considerably increased by the presence in the formulation of hyaluronic acid sodium salt (Hyalastine fraction), which therefore has the effect of promoting percutaneous absorption.

CLAIMS

1. Water-in-oil (W/O) microemulsions containing a retinoid and a phospholipid emulsifier as active ingredient.
- 5 2. Microemulsions as claimed in claim 1, wherein the phospholipid emulsifier is selected from soy phosphatidylcholine and soy lecithin.
3. Microemulsions as claimed in claim 1 or 2, wherein the oily phase consists of alkyl esters of C₁₀-C₂₂ fatty acids.
4. Microemulsions as claimed in claim 3, wherein the oily phase consists
10 of isopropyl palmitate.
5. Microemulsions as claimed in one or more of the preceding claims, wherein the retinoid is selected from isotretinoin (13-cis-retinoic acid), tazarotene and fenretinide.
6. Microemulsions as claimed in claim 5, wherein the retinoid is
15 fenretinide.
7. Microemulsions as claimed in one or more of the preceding claims, also containing sodium hyaluronate.
8. Microemulsions as claimed in one or more of the preceding claims, containing a derivative of hyaluronic acid selected from:
20
 - HA salified with organic and/or inorganic bases with a molecular weight of 50-730 KDa or a high molecular weight (750-1230 KDa);
 - esters of HA with alcohols of the aliphatic, araliphatic, cycloaliphatic, aromatic, cyclic and heterocyclic series;
 - amides of HA with amines of the aliphatic, araliphatic,
25 cycloaliphatic, aromatic, cyclic and heterocyclic series;
 - O-sulphated derivatives of HA up to the 4th degree of sulphation;
 - inner esters of HA.

9. Microemulsions as claimed in one or more of the preceding claims, also containing antioxidants and preservatives.

10. Microemulsions as claimed in claim 9, containing α -tocopherol and parabens.

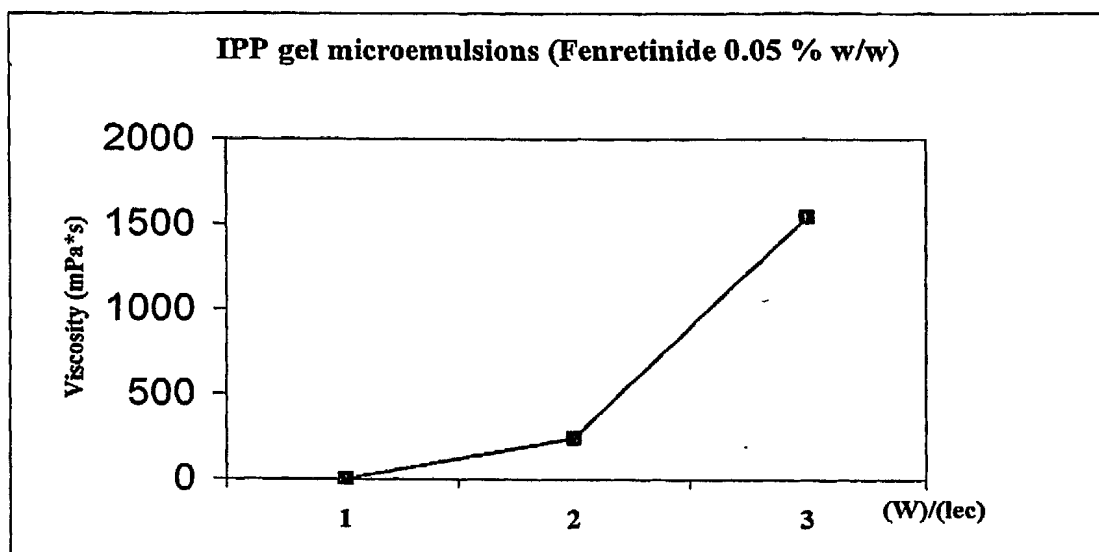
5 11. Pharmaceutical compositions comprising the microemulsions described in claims 1-10.

12. Use of the microemulsions described in the claims 1-10 for the preparation of medicinal products with chemoprotective activity.

10 13. A process for the preparation of the microemulsions claimed in claims 1-10, which involves the addition of a solution of phospholipid emulsifier in the oily phase to the retinoid solution in the same oily phase, or the subsequent addition of an aqueous solution, possibly containing hyaluronic acid, salts or derivatives thereof, preservatives, EDTA and other components.

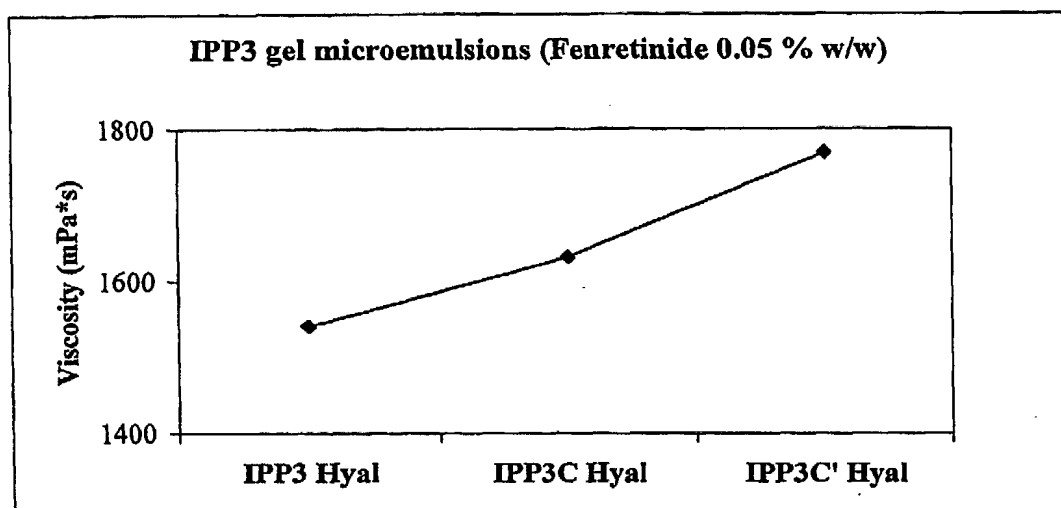
Sheet 1/6

FIGURE 1



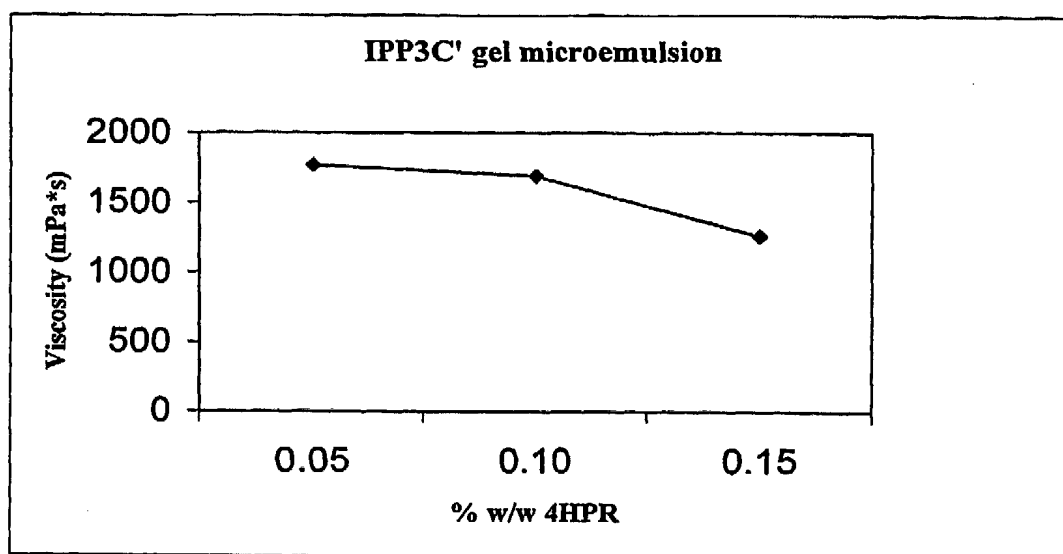
Sheet 2/6

FIGURE 2



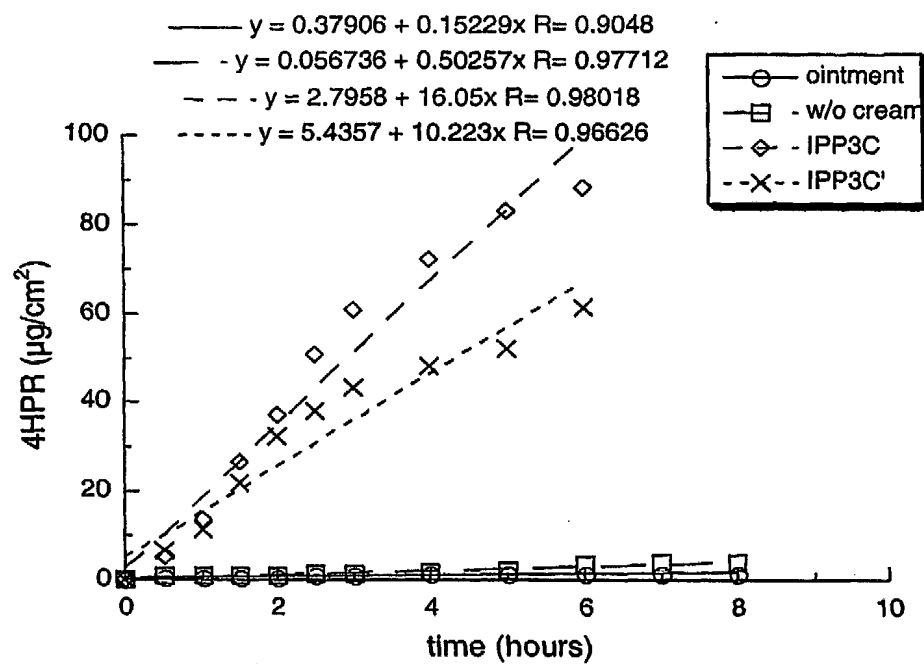
Sheet 3/6

FIGURE 3



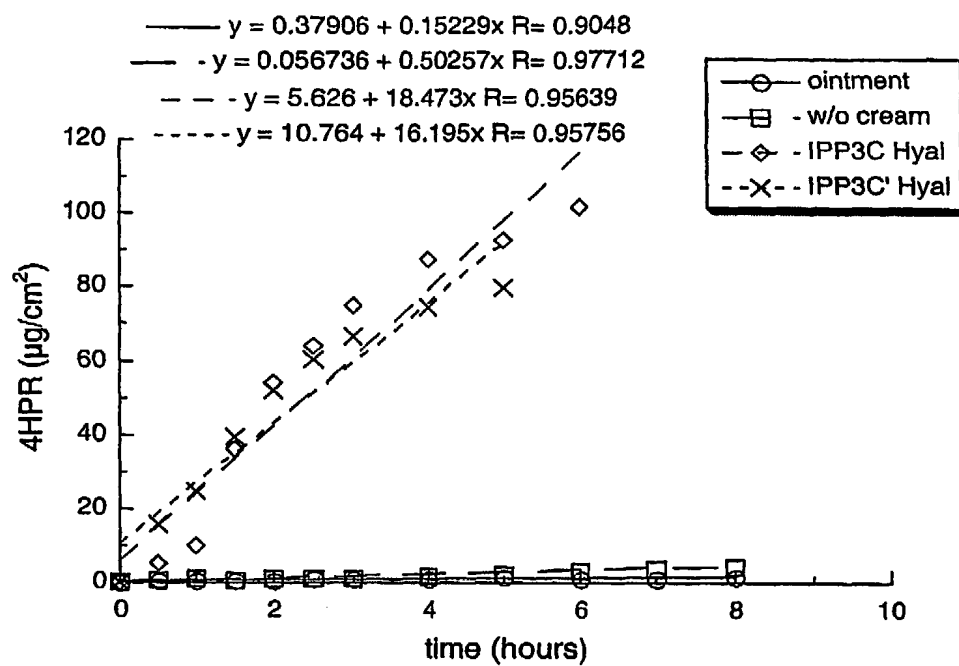
Sheet 4/6

FIGURE 4



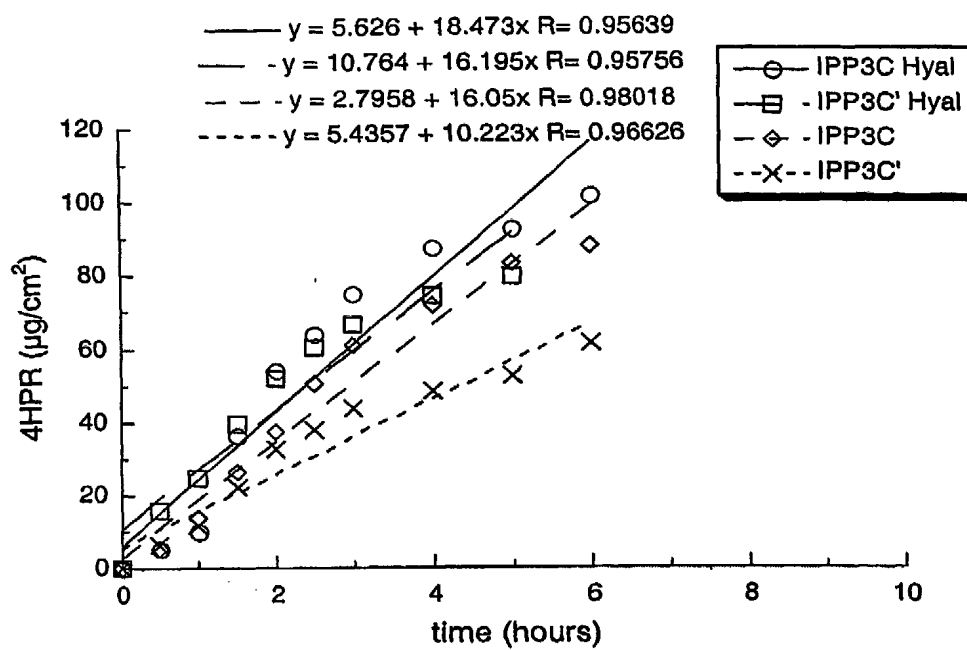
Sheet 5/6

FIGURE 5



Sheet 6/6

FIGURE 6



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/011236

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/10 A61P35/00 A61K31/167 A61K31/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, MEDLINE, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 023 271 A (VIGNE ET AL) 11 June 1991 (1991-06-11) column 8, lines 18-55; examples 5-8	1-3, 11
A	US 2002/102280 A1 (ANDERSON DAVID M) 1 August 2002 (2002-08-01) examples	1-13
A	US 2002/183394 A1 (GUPTA SHANKER ET AL) 5 December 2002 (2002-12-05) examples	1-13
A	PATENT ABSTRACTS OF JAPAN vol. 011, no. 232 (C-437), 29 July 1987 (1987-07-29) & JP 62 045336 A (TOYO BIYUUT KK), 27 February 1987 (1987-02-27) abstract	1-13
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

28 January 2005

Date of mailing of the international search report

15/02/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 681 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Venturini, F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/011236

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PATENT ABSTRACTS OF JAPAN vol. 2000, no. 10, 17 November 2000 (2000-11-17) & JP 2000 204011 A (HUMAN LIMITED:KK), 25 July 2000 (2000-07-25) abstract</p> <p>-----</p>	1-13

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/011236

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5023271	A	11-06-1991	AU 590614 B2	09-11-1989
			AU 6281886 A	10-03-1987
			EP 0232407 A1	19-08-1987
			WO 8701035 A1	26-02-1987
US 2002102280	A1	01-08-2002	US 2004022820 A1	05-02-2004
			AU 1987802 A	11-06-2002
			CA 2428993 A1	06-06-2002
			EP 1345589 A1	24-09-2003
			JP 2004514690 T	20-05-2004
			WO 0243696 A1	06-06-2002
US 2002183394	A1	05-12-2002	EP 1349545 A1	08-10-2003
			WO 02058689 A1	01-08-2002
JP 62045336	A	27-02-1987	NONE	
JP 2000204011	A	25-07-2000	NONE	